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Catalytic Asymmetric Synthesis of 3-Hydroxy-3-trifluoromethyl Benzofuranones via Tandem Friedel–Crafts/Lactonization Reaction

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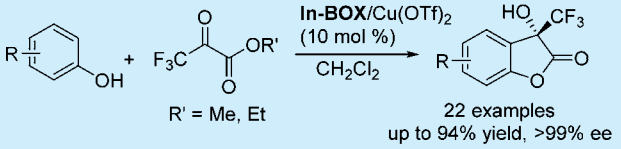
Supporting Information

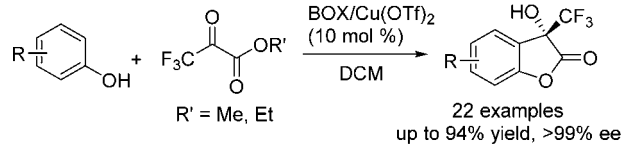
ABSTRACT: A highly enantioselective and regioselective chiral Lewis acid catalyzed tandem Friedel–Crafts/lactonization reaction is reported, providing direct access to plenty of 3-hydroxy-3-trifluoromethyl benzofuran-2-ones in up to 94% yields with up to >99% ee. Mechanistic study reveals that the interactions between the phenolic hydroxyl group and trifluoropyruvate are the most likely contributing factor to the high enantio- and regioselectivity. Optically pure (−)-BHFF can be obtained in gram-scale with 0.05 mol % catalyst, demonstrating the potentially utility of this method in medicinal chemistry.



The 3,3-disubstituted benzofuran-2-one is a prominent common structure, which exists in plenty of biologically active and natural products.[1] Recently, the 3-hydroxy-3-trifluoromethyl substituted benzofuran-2-ones have attracted increasing attention because of their remarkable medicinal and pharmaceutical activities partly due to the unique properties of the trifluoromethyl moiety.[2] For example, 5,7-di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (BHFF) was found to be a strikingly effective GABAB positive allosteric modulator and was demonstrated to have therapeutic potential to treat nervous system disorders.[3] Notably, (−)-BHFF has proven to be more robust than (+)-BHFF and *rac*-BHFF by in vivo studies on Chinese hamsters.[3a] Among the methodologies to establish 3-hydroxy-3-trifluoromethyl benzofuran-2-ones, the tandem Friedel–Crafts/lactonization reaction represents a direct access, which has been studied since the 1980s.[4] In most cases, harsh reaction conditions, for example, using a strong organic acid as solvent at high temperatures, as well as a stoichiometric amount of active species were required. The reason is probably due to the complexing of the exposed phenolic hydroxyl group with the Lewis acid catalysts and poisoning the catalyst. Importantly, of specific interest is to realize the enantio- and regiocontrol to obtain this targeted structure. However, to date, the optically active ones can only be accessed by resolution[3a] and no catalytic asymmetric method has been reported. The establishment of efficient and reliable methodologies to these optically active compounds with simple and economical starting materials is in great demand.

Recently, we found that a simple chiral BOX/Cu(II) catalyst exhibited high efficiency in this tandem reaction, giving a broad range of 3-hydroxy-3-trifluoromethyl benzofuran-2-ones with high levels of enantioselectivity (Scheme 1). In particular, optically active (−)-BHFF was synthesized in gram-scale with 0.05 mol % catalyst. In this letter, we wish to report our efforts on this subject.

Scheme 1. Catalytic and Asymmetric Tandem Friedel–Crafts/Lactonization



As the regioselectivity is usually poor in the reported tandem Friedel–Crafts/lactonization reactions,[4b,c] 2,4-di-*tert*-butylphenol **1a** was first chosen as a model substrate to avoid this problem. Initially, 10 mol % of ^{t}BuBOX(**L1**)/Cu(OTf)$_2$ was employed as the catalyst since it proved to be powerful in the asymmetric Friedel–Crafts reactions of electron-rich aromatics with trifluoropyruvates[5] by Jørgensen and coworkers.[6] Unfortunately, the desired product was obtained in only 27% yield with 40% ee in dichloromethane even after running the reaction for 16 h at room temperature (Table 1, entry 1). The amount of trifluoropyruvates was increased from 1.1 to 11 equiv to speed up the optimization. In this case, the yield of product was greatly enhanced to 83% and the ee value was also improved from 40% to 53% (entry 2). Considering that ligands bearing sterically different backbones may primarily influence the enantioselectivity,[7] we turned to investigate the effects of other ligands. When **L2** and **L3** were used, the lactone product was formed with poor levels of enantioselectivity (entries 3 and 4). A better result was achieved by using ligand **L4** resulting in 77% ee together with a 93% yield (entry 5). Side-armed oxazoline ligand **L5** failed to enhance the enantiocontrol (entry

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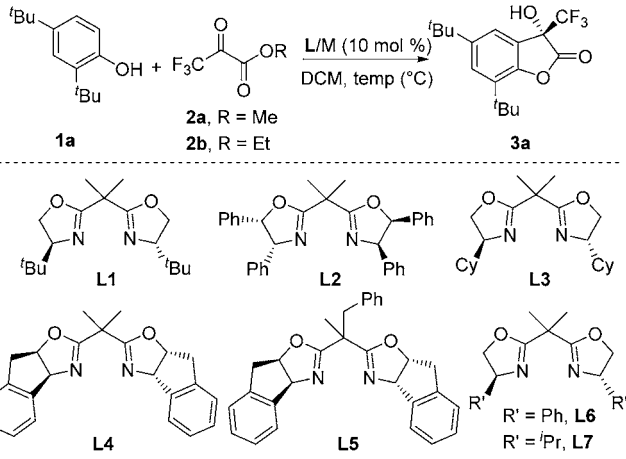
Table 1. Reaction Optimization[a]



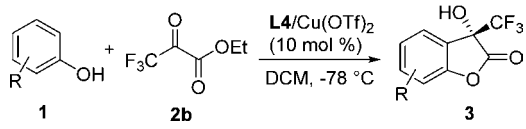
entry	L	M	temp (°C)	t (h)	yield (%)[b]	ee (%)[c]
1[d]	L1	$Cu(OTf)_2$	rt	16	27	40
2	L1	$Cu(OTf)_2$	rt	4	83	53
3	L2	$Cu(OTf)_2$	rt	4	94	45
4	L3	$Cu(OTf)_2$	rt	4	95	47
5	L4	$Cu(OTf)_2$	rt	4	93	77
6	L5	$Cu(OTf)_2$	rt	3	94	69
7	L6	$Cu(OTf)_2$	rt	3	94	11
8	L7	$Cu(OTf)_2$	rt	3	93	30
9	L4	$Cu(ClO_4)_2{\cdot}6H_2O$	rt	2	93	76
10	L4	$Cu(SbF_6)_2$	rt	2	86	56
11	L4	$Ni(ClO_4)_2{\cdot}6H_2O$	rt	2	93	58
12	L4	$Fe(OTf)_3$	rt	2	93	0
13	L4	$Mg(ClO_4)_2{\cdot}6H_2O$	rt	15	75	12
14	L4	$Cu(OTf)_2$	−40	8	92	85
15	L4	$Cu(OTf)_2$	−78	8	93	90
16[e]	L4	$Cu(OTf)_2$	−78	25	94	94
17[e,f]	L4	$Cu(OTf)_2$	−78	25	94	94

[a]The reactions were carried out under a N_2 atmosphere: Lewis acid (0.040 mmol), **L** (0.048 mmol), 0.2 M, DCM (2.0 mL), **1a** (0.40 mmol), **2a** (4.40 mmol). [b]Isolated yield. [c]Determined by HPLC analysis on chiral stationary phases. [d]M/**L** = 1/1.2, 1.1 equiv of **2**. [e]M/**L** = 1/1, 1.5 equiv of **2**, 0.1 M, DCM (4 mL). [f]**2b** was used.

6), and no further improvements on enantioselectivity were engendered by using ligands **L6**−**L7** (entries 7−8). Attempts to improve the enantioselectivity by further screening of Lewis acids were not successful (entries 10−13). The ee value can be slightly increased under a reduced reaction concentration, whereas studies on other solvents could not improve the selectivities.[8] Remarkably, the level of enantioselectivity was increased significantly when lowering the temperature to −40 °C or even to −78 °C, while still maintaining high reactivity (85% ee and 90% ee, entries 14 and 15). Encouragingly, further study showed that 94% ee together with a 94% yield could be obtained even when reducing the amount of trifluoropyruvate from 11 to 1.5 equiv under optimized conditions (entry 16). Changing methyl trifluoropyruvate to ethyl trifluoropyruvate gave a similar result (entry 17).

Under the optimized conditions, the substrate scope of the current protocol was investigated next. As shown in Table 2, substrates **1a**−**1e** with electron-rich substituents at the *para* position on the aromatic ring, bearing a *tert*-butyl group on the *ortho* position at the same time, reacted smoothly. Excellent levels of enantioselectivity and yields were obtained (Table 2,

Table 2. Substrate Scope with Ethyl Trifluoropyruvate[a]



entry	R	t (h)	yield (%)[b]	ee (%)[c]
1	2,4-di-tBu (**1a**)	25	94	94
2	2-tBu, 4-Me (**1b**)	32	80	96
3	2-tBu, 4-OMe (**1c**)	32	81	95
4	2-tBu, 4-Et (**1d**)	48	88	95
5	2,4-ditertpentyl (**1e**)	24	94	94
6[d]	2,4-di-iPr (**1f**)	48	75	99
7[d]	2,4-di-Me (**1g**)	96	51	>99
8[d,e]	2,4-di(2-phenyl)propyl (**1h**)	14	94	92
9[d,e]	2-tBu (**1i**)	120	83	85 (>99/1)
10[d,e]	2-phenyl (**1j**)	120	67	90 (95/5)

[a]The reactions were carried out at −78 °C under N_2 atmosphere: $Cu(OTf)_2$ (0.04 mmol), **L4** (0.04 mmol), DCM (4.0 mL), **1**/**2b** = 1/1.5 (**1**, 0.40 mmol). [b]Isolated yield. [c]Determined by HPLC analysis on chiral stationary phases; in parentheses are regioselectivity of *ortho*/*para* alkylation products. [d]The reaction was carried out at room temperature. [e]2.5 equiv of **2b** were used.

entries 1−5). When substrate **1f** bearing isopropyl groups at both the *ortho* and *para* position was subjected to the reaction, the reactivity decreased while the enantioselectivity can reach up to 99% even with a change to room temperature (entry 6). The presence of a less hindered methyl group at both the *ortho* and *para* position led to a decreased yield but excellent enantioselectivity (entry 7). Substrate **1h** was also tolerated in the reaction, giving an excellent yield and enantioselectivity (entry 8). Further exploration was carried out in terms of the regioselectivity with only one substituent on the *ortho* position of the phenyl ring. To our delight, a Friedel−Crafts reaction proceeds regiospecifically with >99/1 regioselectivity with substrate **1i** and 95/5 regioselectivity with **1j** of *ortho*/*para* alkylation products respectively, giving the lactonization products in good yields and high levels of enantioselectivity (entries 9−10).

The efficiency of this tandem reaction was further investigated with phenols substituted with other alkyl groups. It was observed that phenols with no substituents at the *ortho* position were less reactive, which required a higher temperature and longer reaction time. Methyl trifluoropyruvate was found to give a better yield than the ethyl trifluoropyruvate, probably because the methyl ester is more reactive than the ethyl ester in the lactonization step. For all of these substrates, the levels of enantioselectivity still remain excellent despite moderate yields in some cases (Table 3, **1k**−**1v**). Notably, phenol without any activating substituent can also react smoothly with excellent enantio- and regioselectivity (**1o**). The absolute configuration of the product **3a** was determined by comparing its optical rotations with the literature value;[2b] other products were assigned by analogy.

The practical utility of the current reaction was demonstrated by its application to large scale synthesis of optically active (−)-BHFF (Scheme 2), a remarkable effective $GABA_B$ positive allosteric modulator and a key intermediate in biologically active molecules. Significantly, the catalyst loading can be lowered to 0.05 mol % under the optimized reaction conditions, giving (−)-BHFF in 82% yield with 90% ee. The

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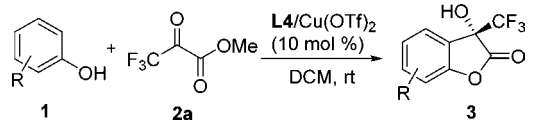
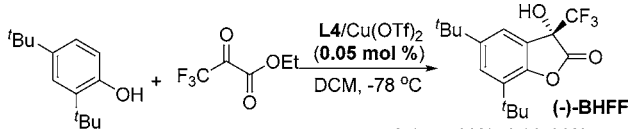
Table 3. Substrate Scope with Methyl Trifluoropyruvate[a]



entry	R	t (h)	yield (%)[b]	ee (%)[c]
1	3,4-(OCH_2O) (**1k**)	120	58	91
2	3,4-di-Me (**1l**)	120	58	>99
3	3,4-di-OMe (**1m**)	120	61	96
4	 (**1n**)	120	75	99
5[d]	H (**1o**)	120	58 (76)	96 (95/5)
6[d]	4-OMe (**1p**)	120	74	95
7[d]	4-^{t}Bu (**1q**)	120	67	98
8[d,e]	4-^{i}Pr (**1r**)	120	61	95
9[d,e,f]	4-(2-phenyl)propyl (**1s**)	120	80	96
10[d,e,f]	4-Ph (**1t**)	120	70	97
11[d,e,f]	4-(4-BrC_6H_5) (**1u**)	120	50	95
12[f]	2,3-di-Me (**1v**)	40	76	97

[a]The reactions were carried out at rt under a N_2 atmosphere: $Cu(OTf)_2$ (0.08 mmol), **L4** (0.08 mmol), **1**/**2a** = 1/1.5 (**1**, 0.80 mmol), DCM (8.0 mL). [b]Isolated yield; yield in parentheses was determined by ^{19}F NMR with $PhCF_3$ as internal standard. [c]Determined by HPLC analysis on chiral stationary phases; in parentheses are regioselectivity of *ortho*/*para* alkylation products determined by ^{19}F NMR with $PhCF_3$ as internal standard. [d]The reaction was carried out at 40 °C. [e]2.5 equiv of **2a** were used. [f]0.2 M, 0.4 mmol scale.

Scheme 2. Gram-Scale Synthesis of Optically Active (−)-BHFF



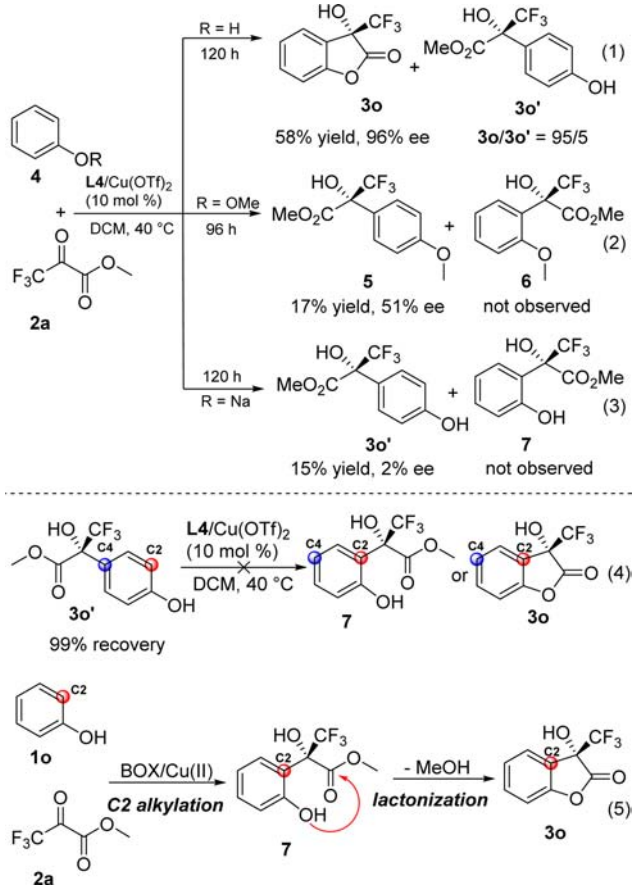
2.14 g, 82% yield, 90% ee
62% yield, > 99% ee
(after recrystallization)

corresponding product can be recrystallized to >99% ee in 62% yield.

The current protocol showed excellent regioselectivity. To fully understand the selectivity, several control experiments have been carried out. As shown in Scheme 3, we had observed minor amounts of alkylation product on the *para* (C4) position with 95/5 regioselectivity in the case of phenol (eq 1). However, when anisole was subjected to the optimal reaction conditions, only the C4-alkylating product was observed with merely 51% ee (eq 2). Similarly, the more nucleophilic sodium phenate gave the C4-alkylating product only in 15% yield with 2% ee (eq 3).

These results showed that the free hydroxyl group in the phenol plays an important role in the regioselectivity. It was also found that the C4-alkylated product **3o′** could not be transformed into the C2-alkylated **7** or the desired product **3o** (eq 4), suggesting that the Friedel−Crafts alkylation is not a reversible process in the present reaction system. Based on these observations, combined with the fact that we have isolated minor nonlactonized intermediates in some substrates,[9] we proposed that the current reaction proceeds via a two-step process as shown in (eq 5). The first step is a Friedel−Crafts reaction in which the selectivity is directed by the H-bond

Scheme 3. Control Experiments and Proposed Reaction Pathway



between the hydroxyl group and trifluoropyruvates, followed by an intramolecular transesterification process.

In summary, a highly enantioselective Lewis acid catalyzed tandem Friedel−Crafts/lactonization tandem reaction has been developed, enabling a direct asymmetric synthesis of plenty of 3-hydroxy-3-trifluoromethyl benzofuran-2-ones from readily available trifluoropyruvates and substituted phenols with up to >99% ee. To the best of our knowledge, this is the first example of a catalytic asymmetric reaction of its version. Mechanistic study suggested that the C2-alkylating pathway is favored with phenolic hydroxyl as the directing group, followed by a lactonization process. Moreover, the newly developed methodology can be applied to gram-scale synthesis of optically active (−)-BHFF with excellent enantioselecitvity with merely 0.05 mol % catalyst loading, which makes it potentially useful in the industrial synthesis of other medicinal and pharmaceutical compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02440.

Condition optimization, experiment procedures, and product characterization (PDF)

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Notes

The authors declare no competing financial interest.

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